Dangerous fluoroquinolones: The urologist's dilemma

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The fluoroquinolone class of antibiotics has been the workhorse of Canadian urologists' strategy in managing simple urinary tract infections (UTIs), complicated UTIs, and bacterial prostatitis. When norfloxacin was introduced in 1983, it was a significant advance compared to trimethoprim-sulfamethoxazole, nitrofurantoin, and the penicillin class of antibiotics for the treatment of uncomplicated UTI. Ciprofloxacin and later levofloxacin were even better antibiotics in terms of treatment of both simple and complicated UTI, as well as prostate and renal infections. Bacteria were becoming resistant to our first-line antimicrobials, while the majority of uropathogens were susceptible to fluoroquinolones, and the cure rate, even in complicated UTI and bacterial prostatitis cases, was very high. We used it for primary treatment, empiric treatment, long-term prophylaxis, and suppression treatment. Although a little disillusioned by the slow rise in fluoroquinolone resistance, urologists in Canada continue to prescribe this class as a go-to antimicrobial strategy for prevention and treatment of UTIs, as well as prophylaxis for invasive urological procedures. Approximately three million prescriptions for fluoroquinolones are issued in Canada every year (2016–2018).

Unfortunately, our love affair with fluoroquinolones is, and should be, ending. They have turned out to be very dangerous for our patients. Bonkat and Wagenlehner[1] recently sounded the alarm. They followed up their opinion piece with an article in *European Urology* in late 2019[2] announcing that the European Commission (EC) had severely restricted the use of fluoroquinolones in all European Union countries. This effectively restricts or bans the use of fluoroquinolones for most urology purposes, including treatment and prevention of uncomplicated UTIs and surgical prophylaxis (including prophylaxis for transrectal ultrasound-guided prostate biopsies). While it is not difficult to assess the impact of that legally binding ruling in Europe, this entire conversation has not appeared to resonate in the Canadian urology community.

Our first warning that everything was not as safe as we assumed was issued by the U.S. Food and Drug Administration (FDA) in 2008 (Table 1). Most urologists are now aware that tendonitis and serious tendon rupture is a recognized safety issue with the fluroquinolones. There are presently more than 2500 lawsuits pending in North America with regard to tendon rupture in the setting of fluoroquinolone use. In 2013, the FDA warned about the risk of disabling peripheral nerve damage with fluoroquinolone use. Then again in 2018, simultaneous FDA notices warned about the serious and significant effects on blood sugar levels and the increased risk of mental disturbances. The hypoglycemia associated with fluoroquinolone use can be life-threatening, while the mental side effects with fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium. The most recent FDA announcement, later in 2018, described an important increase in risk of aortic dissection with fluoroquinolones.

A recently described fluoroquinolone-associated multisystem toxicity syndrome has been recognized in otherwise healthy patients.[3] Patients taking fluoroquinolones for even minor conditions have developed permanent disabling side effects. The description of this syndrome includes disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. Over 100 such cases (up to 2017) involving persistent disabilities have been reported in Canada (1 case per million prescriptions).

So what is our message to our Canadian urology colleagues? Be forewarned, be aware, protect yourself, and most important, protect your patients. We cannot continue to prescribe fluoroquinolones as we have over the last 25 years. However, we cannot simply abandon this class of effective antimicrobial therapy (although many are advocating for that). Rather, we must use them more effectively (e.g., for complicated, life-threatening UTI). We should not use fluoroquinolones empirically without positive culture results; we cannot prescribe long-term (the days of prescribing three months of fluoroquinolones for prostatitis are over); we cannot use as first-line therapy for uncomplicated UTI; and we cannot use as prophylaxis for recurrent UTI in urological surgery. We will have to come up with alternative antibiotics and/or approaches (e.g., transperineal) for transrectal prostate biopsies (Table 2).

Table 1. FDA safety warnings

Date	Warning – Fluoroquinolones are associated with:
July 2008	Tendonitis and tendon rupture
August 2013	Permanent peripheral neuropathy
July 2018	Serious mental disturbances
July 2018	Serious and significant decrease in blood sugar levels
December 2018	Increased risk of aortic dissection

Table 2. Practice changes to protect our patients from the complications of fluoroquinolones

1. Stop using as empiric therapy
2. Do not prescribe for long duration
3. Do not use as first-line therapy for uncomplicated UTI
4. Do not use as prophylaxis for recurrent UTI
5. Do not use as prophylaxis for urological surgery or transrectal prostate biopsies

UTI: urinary tract infection.

The fluoroquinolones can be very effective in many cases of serious and difficult-to-treat UTI. We must choose who we are going to treat with fluoroquinolones carefully and prescribe the correct dose and duration. Urologists must now determine the benefit/harm ratio each and every time we prescribe a fluoroquinolone. Better yet, the patient should be involved in the decision process after being informed of potential risks and complications. We must strive to keep our patients safe.

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